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# Telomeres and Psychological Stress: Perspective on Psychopathologies

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## ABSTRACT

**Introduction:** Telomeres are specialized DNA-protein complexes located at the ends of all chromosomes and act as a "molecular clock" to determine the replicative lifespan of the cells. Recent studies indicate that life-long exposure to stress, starting from the prenatal period, causes many diseases to emerge at an early age, and telomeres may be possible mediators in this process. This article aims to review the relationship between the stress-telomere-disease triad and the potential role of telomere dysfunction in psychopathologies in the light of current literature.

**Methods:** A literature search was conducted along the lines of a narrative review. PubMed and Web of Science databases were used to identify all types of articles published from inception to January 2022. After the title/abstract search, articles available in full text and English were selected based on key findings, the applicability of the method used to test the hypothesis, limitations, interpretation of the results, and impact of the results in the field. A total of 73 records were included in this narrative review.

**Results:** The fact that some age-related chronic diseases, such as cardiovascular diseases and type 2 diabetes, are seen more frequently and at an earlier age in certain psychopathologies including depression, bipolar disorder, and schizophrenia suggests that these disorders are premature ageing syndromes. Although there are some conflicting results in the literature, in line with this hypothesis, the presence of shortened telomeres reported in these psychopathologies and the impact of lifelong exposure to stress on this process are remarkable.

**Conclusion:** Many of the studies point to an association and do not tell much about the causality. Hence, the elucidation of the biological processes underlying the relationship between psychological stress, dysfunctional telomeres and complex, common age-related diseases, as well as psychiatric disorders is important and further studies are needed at the cellular level.

**Keywords:** Accelerated ageing, psychological stress, psychopathology, telomere

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## INTRODUCTION

Telomeres are essential DNA-protein complexes present at the tips of all linear chromosomes, such as human chromosomes, and are responsible for chromosomal stability. As illustrated in Figure 1, human telomeres are constituted by tandemly repeated (TTAGGG) n DNA sequences, which are bound with a large protein complex called shelterin (1). In human somatic cells, the length of telomeres is approximately 10–15 kilo base (kb) and progressively shortens 50–300 bp with each cell division because of the end-replication problem (Figure 2a). Experiencing such gradual shortening of telomeres at each cell division eventually leads to genomic instability and cellular senescence. Hence, telomeres serve as "molecular clocks" that determine the replicative lifespan of our cells (2). The continuing division of human cells necessitates mechanisms to overcome telomere erosion seen in each round of cell multiplication. The telomerase enzyme, a remarkable reverse transcriptase, provides the most widely used mechanism for telomere maintenance. If the cells have plenty of telomerase, there is a balance of lengthening and shortening processes on telomeres so that an average telomere length (TL) is maintained, and the cells can keep dividing. Therefore, TL is closely related to the number of times cells divide and the amount of telomerase activity (2). In humans, telomerase activity is immensely regulated.

### Highlights

- **Telomere shortening may be one of the pathways by which stress 'gets under the skin'.**
- **Stress seems to be linked to shorter telomeres, age-related disorders, and mortality.**
- **Shortened telomeres in certain psychopathologies are striking.**
- **Many of the studies point to an association and do not tell much about the causality.**

Stem cells and germ cells, which are the cells expected to be essentially immortal, have stable telomerase activity throughout their lifespan. Regulated but detectable levels of telomerase activity are found in many normal human adult somatic cells (2). As depicted in Figure 2b, if the cells have some telomerase, the prediction is that since the cells have not completely compensated for the shortening processes, eventually the net

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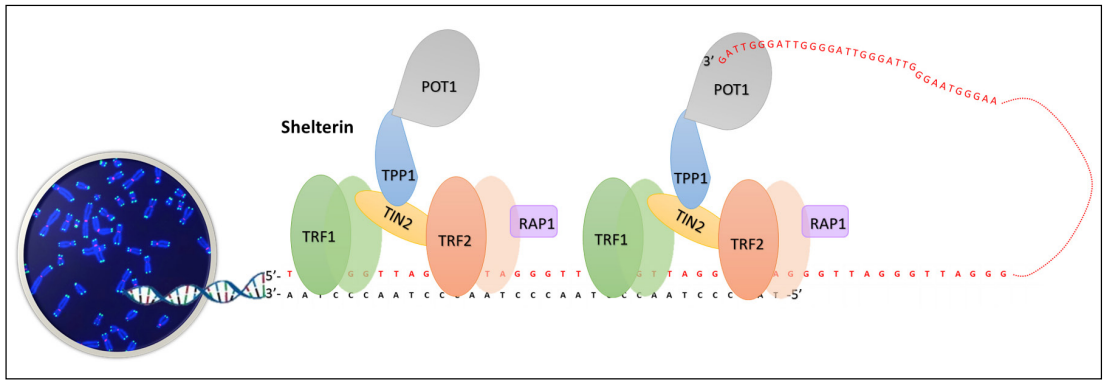


**Figure 1.** Structure of human telomeres. Schematic representation of the six-subunit human shelterin complex bound to double-stranded and single-stranded telomeric DNA.

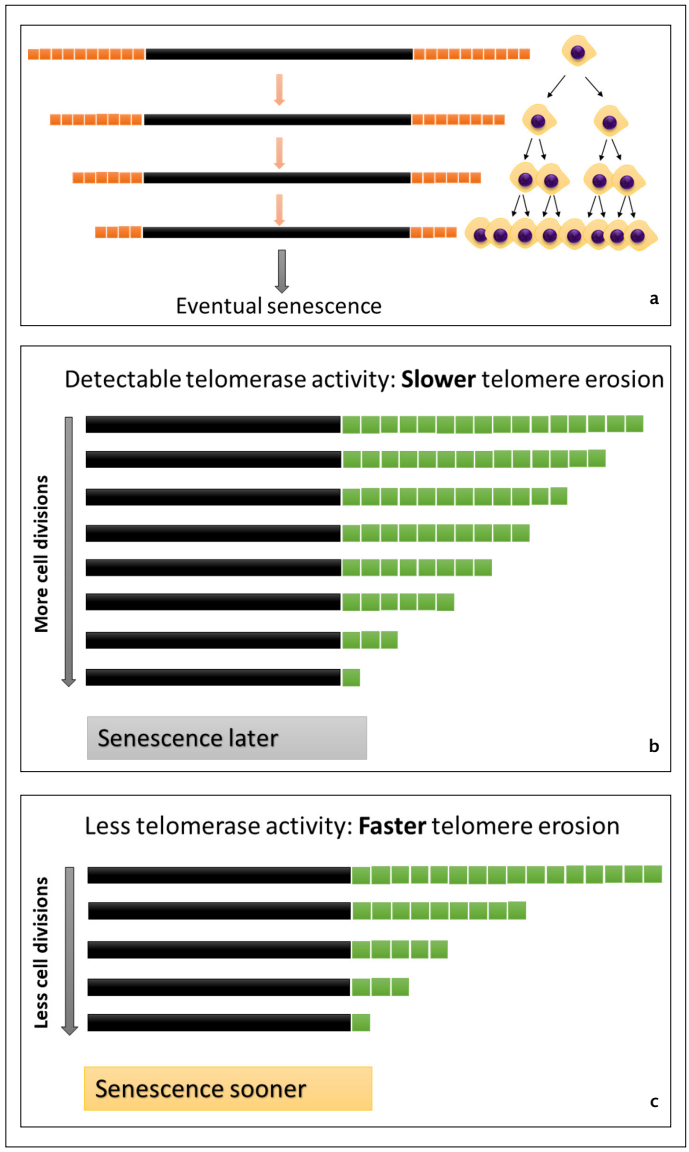


**Figure 2. a–c.** Telomere shortening and cell senescence. Telomeres are depicted as orange and green squares. In human somatic cells, the length of telomeres is approximately 10–15 kb and gradually shortens 50–300bp with each cell division, because of the inability of DNA polymerase to fully replicate the 3′ end of the DNA strand, called the end-replication problem. If this telomere erosion is not balanced by elongation, progressive shortening of telomeres eventually leads to genomic instability and cellular senescence **(a).** Regulated but detectable levels of telomerase activity are found in many normal human adult somatic cells. Since these cells have not completely compensated for the shortening processes, while telomerase might be able to keep up, eventually the net shortening will overcome the elongation by telomerase, and senescence will eventually ensue **(b).** If the cells have less telomerase, then these cells would lose their telomeric DNA faster than the cells having some telomerase and become senescent earlier **(c).**

shortening will overcome the elongation by telomerase, and senescence will eventually ensue. On the other hand, if the cells have less telomerase, then those cells would lose their telomeric DNA faster than the cells having some telomerase and become senescent earlier (Figure 2c). This is important because the normal human body contains certain kinds of stem cells required to keep replenishing the tissues across our lifespan (3).

Telomere length can be determined in all the tissue types that have nucleated cells. Since peripheral blood samples can be obtained non-invasively and easily, TL in blood cells has been studied extensively. Recently, Demanelis et al. (2020) have characterized variability in TLs from >20 tissue types including blood and non-blood tissues. They have shown that TL, in general, is positively correlated across different human tissue types, which may strengthen the use of blood leukocyte TL as an indicator of TL in certain tissues in large epidemiological studies (4). The TL findings cited in this review are leukocyte TL, unless indicated otherwise. Telomere shortening at each cell division can be monitored *in vivo* by measuring TL of people at different ages, supporting the findings on progressive erosion of the telomeres with increasing age (5). The average human TL is 10–15 kb, nevertheless, there is a wide inter-individual variation. This variation is influenced by both genetic and environmental factors. Sib-pair and twin studies have indicated a heritability estimate of TL between 34–82% (6). Genome-wide association studies (GWASs) have identified several loci associated with TL (7), however, GWASs have been able to explain only a small proportion of the variation among individuals. Several environmental factors have been shown to affect TL including smoking, physical activity, lifestyle, and sleep and are reviewed elsewhere (8).

The goal of many researchers in recent years has been to apply all the cellular and molecular information that we have been obtaining about telomere biology towards answering questions on such issues as how we age and what the relationship between telomeres, stress induced accelerated aging and certain diseases is. It should be noted that even ageing alone is a multifaceted process and therefore, there will not be a single answer to these questions. However, one particular aspect of ageing is that there is an increased susceptibility to certain chronic diseases, including cardiovascular disease (CVD), myocardial infarction, type 2 diabetes mellitus (T2DM), vascular dementia, obesity, insulin resistance, Alzheimer's disease, osteoporosis, rheumatoid arthritis, multiple myeloma and cancer (9). Recent studies have supported that these disorders are associated with telomere shortening (10). In other words, if one has short telomeres, he/she may be at risk of these age-related diseases (9,11). As mentioned previously, TL decreases steadily with age, but it is quite remarkable that there is a huge amount of heterogeneity within the human population in terms of TL. For instance, if we measure the TL of a 20-year-old and a 70-year-old person, we may find the same TL. Therefore, TL is not so determinative that we can say for sure if a person has a certain TL there is a particular effect. However, in a given population, those individuals that have the shortest telomeres are at risk for age-related diseases. Alder et al. (2018) have shown this by

modelling the heterogeneity in the population with confidence intervals. Any individual that falls below the first percentile may be at risk of those diseases (12). However, it is important to point out that we cannot say 'what came first' or 'what caused what': telomere shortening or disease.

There is growing evidence that psychological stress is one of the major risk factors contributing to human health and ageing, and causes age-related disorders to be seen at earlier ages including T2DM, metabolic syndrome, CVD, autoimmune disorders, and cancer (13). However, the biological mechanisms through which psychological stress affects normal physiology and leads to certain diseases have yet to be clarified. In order to develop strategies that would alleviate the negative impacts of stress on human health, we need to have a deeper understanding of these pathways. In recent years, psychological stress-induced accelerated ageing has appeared to be one of the most important players. It is known that a major facet of biological ageing is ageing at the cellular level (14). Over the last two decades, telomeres have emerged as biomarkers for cellular ageing. At the same time, it has been revealed that telomeres are also important mediators through which chronic psychological stress leads to diseases including psychiatric disorders (15). In line with this, a remarkable number of studies analyzing TL in different disease conditions have been carried out in order to elucidate the possible link between a wide range of stressors, accelerated ageing and disease etiologies. This article aims to review the relationship between the telomere attrition-stress-disease triad, with a particular focus on the implications of telomere dysfunction in psychiatric disorders.

## METHODS

For the present study, a literature examination was conducted along the lines of a narrative review research (16). PubMed and Web of Science databases were searched to identify all articles published from inception to January 2022 containing the keywords 'telomere' and 'accelerated ageing' along with any of the following keywords: 'psychological stress', 'depression', 'bipolar disorder', 'schizophrenia', 'anxiety disorder', and 'posttraumatic stress disorder'. All types of articles and all studies that used human subjects, animals and *in vitro* studies were included. Articles not available in full text and not in English were excluded. After an initial title/abstract screening, articles were critically evaluated and selected based on key findings, the applicability of the method used to test the hypothesis, limitations, interpretation of the results, and implications of the conclusions in the field. Additional references were identified from the articles retrieved during the first round of research by manual searching among the cited references. In addition, care was taken to include the original landmark studies and current meta-analyses on the subject and to limit references from the same research group or the same journal. Articles with a limited reference list were also excluded.

## RESULTS

The number of records identified through database searching was 674 for PubMed/Medline and 659 for Web of Science. After an initial title/abstract screening, full-text publications were reviewed for potential inclusion (n=107), and eight additional references were identified from the articles retrieved during the first round of research by manual searching among the cited references. Forty-two studies were excluded for limited number of references, and being from the same research group or the same journal. Seventy-three records were included in this narrative review.

### Psychological Stress and Telomeres

The association of TL with both a healthy lifespan and mortality risk has been studied extensively and is well established, but the processes that cause this relationship are yet to be determined. For example, Njajou et al. (2009) have shown that longer telomeres are associated with an increased number of years of healthy life (11). On the other hand, a very interesting observation in a cohort of 143 unrelated people aged >60 years and followed for 17 years has shown that short TL is associated with higher mortality rates. Specifically, shorter telomeres were associated with 3.2 times higher number of deaths from heart disease and 8.5 times higher number of deaths from infectious diseases (17). Similarly, a meta-analysis of 121,749 individuals with 21,763 cases of death has shown that short telomeres are associated with an increased risk of all-cause mortality in the general population (18).

The relationship between exposure to psychological stress and poor health outcomes is becoming more apparent. Particularly, psychosocial stress emerges as one of the major risk factors for the early onset of common and complex age-related disorders (19). Recent research has highlighted the important role of telomere shortening as a possible underlying pathway relating exposure to psychosocial stress to the risk of many disorders (20). As human beings, we are exposed to different sources of stress (i. e. stressors) such as psychological stress in our lives and can give physiological stress responses the mechanisms whereof are quite well established. However, the mechanisms of how psychological stress affects our cells, how stress prematurely ages our cells and how it makes us more prone to diseases are less known. What is known is that when stressors are chronic, they can cause a lot of biological wear and tear. There have been several studies showing that stress is associated with earlier mortality. For instance, Schulz and Beach (1999) have reported that caregivers are as likely to live as long as those in the control group, but caregivers who are experiencing mental or emotional strain are 63% more likely to die within four years (21).

For the first time, Epel et al. (2004) have analysed the effect of chronic psychological stress on telomeres. To do so, they have compared three markers of cellular ageing (telomerase activity, TL, cellular oxidative stress) in 58 healthy premenopausal women, who were biological mothers of healthy children or children with a chronic disease. Both perceived stress assessed by a 10-item questionnaire and chronicity (i.e. years of caregiving) were found to be associated with shorter telomeres, higher oxidative stress, and lower telomerase activity. They have suggested that women with the highest levels of perceived stress had shorter telomeres on average equivalent to 9–17 years of additional ageing compared to women with low stress (22). This finding has been replicated in different states of chronic severe distress. For example, chronic caregiving stress has been linked to shorter TL in older men and women who were caregivers of Alzheimer's disease patients. Besides having shorter telomeres, these people were also found to have significantly lower T cell proliferation than control groups, but present a higher production of immunomodulatory cytokines (TNF-$\alpha$ and IL-10) in response to *in vitro* stimuli (23). Humphreys et al. (2012) have examined TL in 61 women who had experienced chronic stress due to intimate partner violence and found significantly shorter telomeres in previously abused women compared to those in the control group (n=41). In addition, they have indicated that length of time in an abusive relationship and having children is related to shorter TL (24).

Shorter telomeres have been consistently reported in healthy people without a current diagnosis of psychiatric disorder but who have been exposed to adversity in their childhood (25). Thus, not only the stress in adulthood but also the stress in the early development environment, such as childhood maltreatment (e.g., sexual assault, physical abuse, suffering from neglect) may be linked to shorter telomeres, age-related disorders, and mortality in adult life. O'Donavan et al. (2011) have shown that people with post-traumatic stress disorder (PTSD, n=43) have shorter telomeres when compared to those in the control group (n=47). In the same study, authors have investigated childhood trauma and reported that childhood trauma seemed to account for the PTSD group's difference in TL (26). A

recent meta-analysis of 41 studies involving 30,773 individuals supports the type of early childhood adversity and timing significantly associated with shorter TL and that these may contribute to disease risk and physiological ageing (27). It is thought that the effect of stress on TL may go back even further than childhood since adult health is in part determined by prenatal programming. Entringer et al. (2011) have compared the TLs of healthy young adults whose mothers had experienced a severe stressor in the index pregnancy (n=45) to the control group (n=49) whose mothers had a healthy, uneventful index pregnancy. They have shown that even though all the adults were healthy and non-depressed, the mothers who had prenatal stress had offspring with shorter telomeres as adults when compared to the control group (28).

In a meta-analysis by Schutte et al. (2016), shorter TL was found to be significantly associated with perceived stress in 1143 individuals, even though there were significant moderators including effect size differences between female-only and mixed-gender samples (29). Epel et al. (2006) have investigated whether TL and telomerase in leukocytes are associated with CVD risk factors and physiological signs of stress arousal in healthy women (n=62). They found that people with long telomeres tended to have very little acute mental stress reactivity when they were exposed to standardized laboratory stressors (i.e. TRIER's social stress test). In contrast, low telomerase activity and short telomeres in leukocytes were associated with excessive autonomic response to acute mental stress and elevated levels of epinephrine. In addition, it has been found that low telomerase activity is associated with the main risk factors for CVD, such as poor lipid profile, increased systolic blood pressure, high fasting blood glucose, increased abdominal obesity, and smoking (30). That study was the first to support the idea that the process of coping with stress is important and is linked to telomeres. Stress-mediated telomere attrition in both prenatal and postnatal life has also been confirmed by several meta-analyses (31) and was replicated in experimental animal models (32).

**Telomere Dysfunction in Psychopathologies**

The idea that telomeres might play a role in human disorders came from an understanding of a rare inherited human disease called dyskeratosis congenita (DC). This disease is frequently caused by mutations in telomerase and is characterized by severely short telomeres (33). The high premature mortality rate of the disease is mostly due to bone marrow failure, an exhausted immune system, and other organ failures. A possible mechanism might be that stem cells or the cells that arise from stem cells in the immune system lose their ability to proliferate all the way through a normal life expectancy. Not limited to DC, a group of other related genetic diseases that are caused by impairments in telomere maintenance, such as Werner's syndrome and idiopathic pulmonary fibrosis are collectively called 'telomeropathies', 'telomere disorders', or 'telomere syndromes'. Readers can refer to the recent review by Grill and Nandakumar (2021) for more detailed information (34). An interesting study by Rackler et al. (2012) showed that patients with DC may exhibit neuropsychiatric disorders more frequently than the general population or other individuals with chronic diseases (35). Although rarely reported, the comorbidity of psychiatric disorders in Werner's syndrome is quite remarkable. Barak et al. (2001) have reported two Werner's syndrome cases of a mother and a son who represented resistant psychosis (36). All of these findings from human genetic telomere disorders support a possible role of short telomeres not only in the development of certain somatic diseases but also in the development of psychopathologies. Animal studies also provide evidence for the possible relationship between telomere biology and psychopathology development. It has been shown that chronic mild stress exposure in mice results in reduced telomerase activity in the hippocampus and this can be resolved by antidepressant fluoxetine treatment. Moreover, inhibition of telomerase by 3'-azido-deoxythymidine treatment led to depression-like behaviour and disturbed hippocampal neurogenesis (37).

Several mental disorders, such as major depressive disorder (MDD), bipolar disorder (BD), schizophrenia (SCZ), post-traumatic stress disorder (PTSD), and anxiety disorders are associated with an increased risk of serious somatic medical conditions. Recent prospective studies have supported that age-related disorders, such as T2DM, obesity, hypertension, dyslipidemia, CVDs, and neurodegenerative disorders are more common in patients with these psychiatric conditions and they manifest earlier than in the general population (38,39). Based on these observations, a group of researchers have recently hypothesized that certain psychiatric illnesses are syndromes of accelerated ageing (40). TL-based studies of accelerated ageing in psychiatric patients have recently attracted attention and there is a considerable literature examining the possible link between psychopathology and shorter telomeres by assessing cases versus control groups.

Based on the evidence for aberrant stress response in depression, for the first time, Simon et al. (2006) have tested accelerated ageing in mood disorders by measuring TL in chronic mood disorder patients (n=44) and age-matched control groups (n=44). They have reported significant telomere shortening in mood disorders, suggesting approximately 10 years of accelerated ageing. However, one of the most important limitations of this study is that confounding factors (e.g. current/past medication use) were not taken into account, which may affect TL (41). Wolkovitz et al. (2011) have analyzed the TL in medication-free patients with MDD (n=18) and reported that shorter TL is correlated with chronicity, inflammation and oxidative stress parameters (42). Nevertheless, the sample size of that study is quite limited. In a large longitudinal cohort containing 1,095 current MDD patients, 802 remitted MDD patients and 510 control subjects, it has been reported that the most severe and chronic MDD patients demonstrated the shortest TL among the three groups. Remitted MDD patients also had a significantly shorter TL than control groups, and the difference persisted after adjustments for health and lifestyle variables. On the other hand, current and remitted patients had similar TL (43). In a recent study by da Silva et al (2022), TL and telomerase activity were examined in patients with MDD (n=12) both before and after treatment with selective serotonin reuptake inhibitors (SSRIs) and were compared to the control group (n=12). They have reported that before the SSRI treatment, patients exhibited shorter TL and lower telomerase activity than control subjects. Interestingly, after 24 weeks of SSRI treatment, both TL and telomerase activity increased, approaching the values in the control group (44). However, the sample size of that study was quite limited, and almost all the participants were women. The largest depression study, in which 11,670 Chinese women were examined, has supported that shorter TL was associated with adverse life events. In particular, TL has been found to be significantly shorter in those who experienced more stressful life events or reported childhood sexual abuse (45).

Bipolar disorder also seems to be an accelerated ageing syndrome and is among the psychopathologies included in TL studies. Elvsashagen et al. (2011) have analyzed short telomere load (i. e. TL <3 kb) and mean TL in BD type 2 patients (n=28) and control subjects (n=28). They have reported that short telomere load is significantly higher in patients, which may be equivalent to 13 years of additional ageing. In addition, the study found that people with shorter telomeres are more likely to have depressive episodes in their lifetime, while shorter TL was not linked to disease duration (46). In a very recent study, significantly shorter TL has been replicated in patients with BD (n=130) as compared to healthy control subjects (n=78) (47). Martinsson et al. (2013) conducted the first study investigating the impact of long-term lithium treatment on TL. Interestingly, they have shown that compared to the control group (n=139), TL of the BD patients (type 1 or type 2; n=256) treated with lithium –either in combination or as mono-therapy– were 35% longer. In addition, their results have indicated an inverse relation between longer TL and the number of depressive episodes (48). However, contradictory

results have been reported in the literature, indicating no association between lithium therapy and longer TL (49).

When we look at the studies examining TL in psychotic disorders, we face a more complex picture mostly due to the confounding effects of antipsychotic medications, which may have a potent effect on telomere biology. Compared to the general population, individuals diagnosed with SCZ have a higher frequency of chronic medical disorders and an earlier onset, which can reduce life expectancy by an average of 15–25 years (40). This suggests that accelerated ageing and telomere dysfunction may have a role in patients with SCZ as well. Comparing the TL of SCZ patients (n=31), unaffected family members (n=24), and unrelated control subjects (n=41), Kao et al. (2008) have found that TL was significantly shorter in patients, regardless of antipsychotic use and disease duration. However, any somatic or psychiatric comorbidities and clinical phenotypes of SCZ were not evaluated in that study (50). In a study conducted by Fernandez-Egea et al. (2009), a group of non-affective psychosis patients (n=41) have been found to have shorter TL and increased pulse pressure compared to the control group (n=41) (51). In chronic SCZ, Yu et al. (2008) have examined the association between TL and antipsychotic treatment response, which was determined based on the Global Assessment of Functioning (GAF) scores of the patients. To this end, they have measured TLs of both SCZ patients (good responders, n=34; poor responders, n=34) and healthy control subjects (n=76) and found that patients with poor response had shorter TL compared to the control subjects (52).

In order to replicate the short TL findings in SCZ, Nieratschker et al. (2013) have conducted a study with a large sample size involving 539 SCZ patients and 519 population-based control subjects. Unexpectedly, they have shown that SCZ patients presented longer TL, particularly in the younger cases. They have also found no association between TL and severity of the disease (53). Although that study has a relatively large sample size, an important limitation was that lifestyle factors have not been adequately addressed. Mansour et al. (2011) have reported no significant difference in TL between SCZ patients (n=60) and control subjects (n=60) after controlling for age and gender (54). In a recent study, we have tested if short telomeres are associated with psychometric psychosis liability and if childhood adversities play a moderating role in telomere attrition by examining a group of SCZ patients, their unaffected siblings and non-clinical control subjects (55). We have found no significant difference in TL between SCZ (n=100) and control (n=100) groups. Interestingly, our results indicated that a telomere shortening was inversely associated with psychosis-like symptoms across all subscales, such as depression, positive symptoms, and negative symptoms, which was independent of clinical diagnosis. Remarkably, the experience of childhood maltreatment and stressful life events have been reported to be associated with the subsequent manifestation of mental psychotic disorders (56), both of which are considered to be common dimensional risk factors for shorter TL. In our study, we have found a substantial excess of childhood adversities among SCZ patients and their healthy siblings. So much so that, both SCZ patients and their healthy siblings had a 5-fold increase in childhood trauma experience compared to the control group. Especially, loneliness between ages 0 and 11 was prominent to be negatively associated with TL (55).

Posttraumatic stress disorder is another psychopathology thought to involve an accelerated ageing process and is being investigated in the context of TL. Avetyan et al. have reported that war veterans with PTSD (n=41) had 1.5 times more shortened telomeres compared to the 49 age-sex-matched healthy individuals without a family history of any psychiatric disorders. They have also analyzed the association between PTSD and certain genetic polymorphisms located on genes that encode telomerase components. They have found that rs2736100 was significantly associated with PTSD. The results of that study are quite remarkable since it has standardized the subjects in terms of exposure to the same stressor. However, its small sample size and recruitment of only male subjects are important limitations (57). Boks et al. (2015) have performed a follow-up study involving 96 males with combat exposure in order to test if there is a positive correlation between trauma exposure and short TL. Surprisingly, their results showed that increased PTSD symptoms are significantly correlated with longer telomeres (58). A meta-analysis of 5 studies involving 3,851 individuals has underlined the association between PTSD and short TL, which is thought to have implications for the prevention of negative health outcomes in the future (59).

Anxiety disorders are also considered as a premature aging syndrome, since they increase the risk of developing several somatic disorders associated with aging. In a study by Verhoeven et al. (2015), TL analysis was performed in current anxiety disorder patients (n=1283), remitted patients (n=459) and 582 control subjects to test the association between TL and anxiety status. Their results have indicated that patients with a current anxiety disorder showed significantly shorter TL, even after adjustments for other confounding factors such as lifestyle, demographics, and MDD comorbidity. Moreover, there was no difference between remitted patients and control subjects in terms of their mean TL (60). A meta-analysis of 19,424 individuals from 17 different studies have also supported that people with an anxiety disorder had shorter TL (61). On the other hand, Kananen et al. (2010) have reported similar TL in a mixed group of individuals suffering from anxiety disorder (n=321) and healthy control subjects (n=653) (62). A large meta-analysis of data from 14,827 people with unipolar and bipolar depression, anxiety, and psychotic disorders have indicated significantly shorter TL for all disorders examined. Authors have pointed out that even though not significantly different, the effect sizes were relatively large for PTSD, anxiety disorders, and depressive disorders, but relatively small for psychosis and bipolar disorder (63).

## DISCUSSION

All of the above findings reviewed so far and also other studies that we could not mention here have provided an important indicator demonstrating that telomere dysfunction may be one of the important pathways through which stress "gets under the skin" leading to premature ageing, diseases and mortality. However, many of the studies point towards an association and do not tell much about the causality. Hence, the elucidation of the biological processes underlying the relationship between psychological stress, dysfunctional telomeres and complex, common age-related diseases as well as psychiatric disorders is important and of considerable ongoing interest.

It is obvious that the discussed relationships are quite complex. As described so far, chronic stress, anxiety, depression, and trauma exposure are all associated with shorter telomeres, which is a measure of cellular ageing. We know that the major outcome of the stress response is the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which eventually leads to a surge of glucocorticoids in the systemic bloodstream. A meta-analysis by Jiang et al. (2019) has supported that the cortisol reactivity to acute psychosocial stress was negatively correlated with TL (64). *In vitro* studies also confirmed that cortisol exposure has a negative effect on telomerase activity in CD4 and CD8 positive T cells (65). Moreover, glucocorticoids have been linked to increased metabolic rates and mitochondrial activity, both of which are known to be associated with increased levels of reactive oxygen species (ROS) (66). It has been shown that increased glucocorticoids may upregulate the expression of pro-inflammatory cytokines, while downregulating anti-inflammatory mediators (67). In an *in vitro* cell culture study by Butler et al. (2012), it has been shown that the expression of shelterin complex subunits are altered after dexamethasone and TNF-alpha treatment. They have suggested a possible link between telomeric proteins and mediators of stress and inflammation (68). Telomeric DNA is thought to be more prone to be

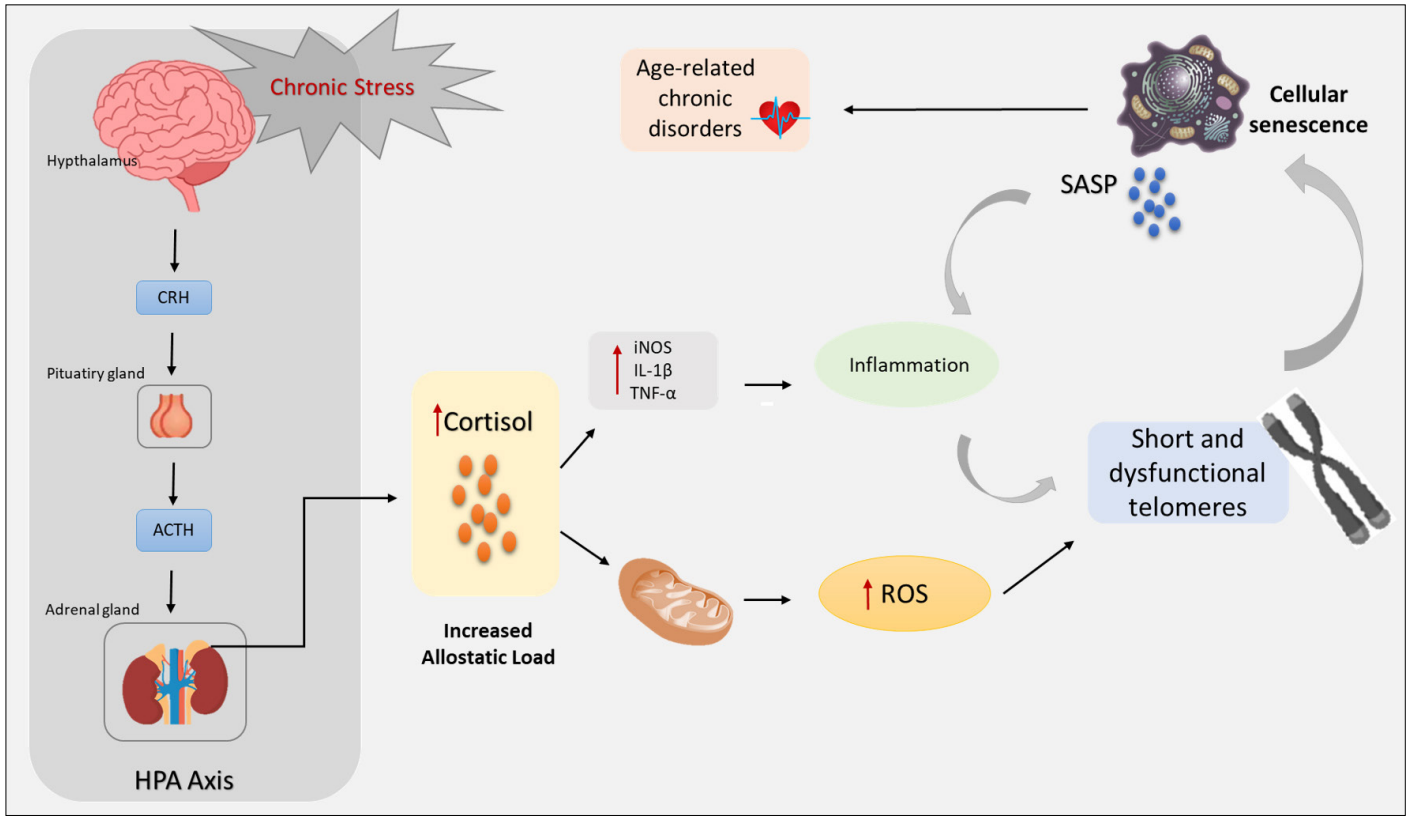


**Figure 3.** Schematic overview of molecular and cellular pathways linking psychological stress to short and dysfunctional telomeres, and age-related chronic disorders (ACTH: Adrenocorticotropic hormone; CRH: Corticotropin-releasing hormone; HPA: Hypothalamus-Pituitary-Adrenal; ROS: Reactive oxygen species; SASP: Senescence associated secretory phenotype).

damaged by ROS since it is composed of Guanine-rich sequences (69). In addition, it is suggested that the existence of shelterin on telomeres counteracts the recruitment of proteins required for DNA damage repair in response to single-strand DNA breaks induced by ROS, thereby leading to inefficient DNA repair at telomeres (70). Therefore, ROS produced by stress exposure and/or inflammation preferentially damage telomeres and inhibit telomerase, which eventually results in short and dysfunctional telomeres. Another pathway thought to be involved in this scenario is increased inflammation induced by the stress hormone glucocorticoid. Inflammation causes short and dysfunctional telomeres followed by cell senescence. It has been shown that senescent cells present a pro-inflammatory phenotype (a.k.a. senescence-associated secretory phenotype). Therefore, there may be positive feedback control that leads to a vicious cycle of increased inflammation and dysfunctional telomeres (Figure 3), which is reviewed elsewhere (15).

Studies have provided strong evidence that chronic stress is causing lower amounts of telomerase and shorter telomeres, which eventually reduce the ability of stem cells to replenish themselves and result in several age-related disorders. Lifetime stressors, such as caregiving, maternal stress, and early life adversity stimulate the HPA axis and immune and autonomic systems to generate responses to the organism's adaptation to these conditions. Elevated levels of stress hormones and inflammatory cytokines due to exposure to chronic stressors and life events disrupt the allostasis and lead to an increase in the allostatic load (71). We know that some individuals may have a lower cellular allostatic burden than others even when they are exposed to the same stressors, which suggests the presence of resilience factors. Recent research has suggested TL might be a candidate biomarker revealing inter-individual differences in terms of their ability to cope with stressors. It seems that psychological stress resilience and healthy lifestyle factors may prevent persons from premature telomere attrition; in fact, all of these are associated with longer TL (72). On the other hand, high vulnerability to stress, an unhealthy lifestyle, and poor social interactions has been linked to elevated allostatic load and, ultimately, accelerated telomere erosion (73).

Shortening of telomeres in certain psychopathologies is striking, suggesting that these disorders are syndromes of accelerated ageing. Additional research on the general mechanisms responsible for psychopathologies and how they impair telomere biology and vice versa would certainly be illuminating. Longitudinal studies with systematic approaches are warranted and methodological advances in measurements for TL also require attention. For psychopathologies, there are several confounding factors such as psychiatric and other medical comorbidities (e.g. substance abuse), and the use of a number of psychiatric/non-psychiatric medications should be taken into account to highlight the importance of TL. Translational "from bench to bedside" studies are needed to reveal potential mechanisms. These studies would contribute to our understanding of the role of telomeres in human health and ageing, as well as in resilience to stress that would have important implications for prevention and intervention approaches.

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